PRE-ECLAMPSIA SCREENING/ PREDICTION ASSAYS

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Pre-eclampsia: background

- Pre-eclampsia (PE) is defined as recent onset hypertension (arterial pressure ≥ 140/90 mmHg for 2 measurements at 4hr interval) and proteinuria (≥ 300 mg/24hr) after 20 weeks amenorrhea (WA) in *a priori* normotensive women.
- Early onset (between 20 and 34 WA) is associated with a less favourable prognosis with higher fetal and maternal risks.
- Pre-eclampsia is still a leading cause of maternal and perinatal mortality and morbidity in Ireland.
- In Ireland PE affects from 2 to 3% of all pregnancies, and 5 to 7% of nulliparous women. It accounts for 20 . per cent of all neonatal intensive care unit (NICU) admissions. [1]
- In severe forms (10% of cases), maternal, fetal and/or neonatal complications can develop rapidly with serious complications and a potentially fatal prognosis.
- Induced delivery may be proposed by the clinician based on the clinical signs of the patient and the impact on the fetus.

Every year 2,000 pregnant women in Ireland are affected by PE.

Assays of pre-eclampsia biomarkers can be used for:

- **SCREENING in the 1st trimester of pregnancy: identifying patients at risk of developing pre-eclampsia who could benefit from preventive measures (for example, treatment with 150-160 mg aspirin implemented 16 WA)[2] and/or intensive out-patient monitoring.**
- **NEW PREDICTIVE in the 2nd semester of pregnancy: allows prediction or exclusion of pre-eclampsia several weeks in advance of its onset so that early care can be provided to prevent complications or the patient can be reassured and kept at home.**

Screening in 1st trimester (11^{+0} to 13^{+6} WA) [3-5]

Benefits

- Establish close obstetric monitoring
- Initiate aspirin therapy at low doses before 16 WA

Risk calculation

"PE risk" patients can be screened for the presence of risk factors with the Doppler measurement of the pulsatility index (PI) of the uterine arteries (UAD), mean arterial pressure (MAP) and the assay of PAPP-A and PlGF biomarkers.

Risk factors incorporated in the calculation

- BMI
- Geographical origin
- Parity
- Personal or family history of PE
- Chronic high blood pressure, treated or not
- Smoking

Risk calculation

In 2013, the Nicolaides team (Akolekar *et al*, 2013) has published a study with 58,884 single pregnancies, 2.4% of which with PE. The detection rate is better for early PEs and, compared to purely clinical information, the combination of biophysical and biochemical data significantly improves the detection rate.

PE detection rate by risk analysis (after Akolekar, 2013)

Parameters	PE with birth <34 weeks		PE with birth <37 weeks		PE with birth >37 weeks	
	FP 5 %	FP 10 %	FP 5 %	FP 10 %	FP 5 %	FP 10 %
Clinical data	35,5 %	50,5 %	32,7 %	43,3 %	29,4 %	40,3 %
with PlGF, PAPP-A, UAD & MAP	93,4 %	96,3 %	61,1 %	76,6 %	37,8 %	53,6 %

The same team published a new study at the start of 2016 of 35,948 pregnancies (O'Gorman *et al*, 2016), 2.9% of which with PE, using a new calculation method. The combination of clinical information with PlGF, PAPP-A, UAD and MAP enables screening, with 5% false positives, of 82% of PEs before 32 WA (42% with only maternal risk factors); the detection rate is 59% for PEs between 32+0 and 36+6 WA and 37% between 37+0 and 39+6 WA (34% and 31% respectively with only maternal risk factors).

NEW | PREDICTIVE TEST

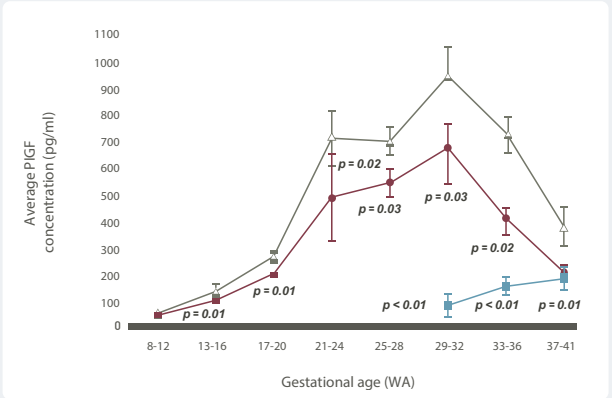
Predictive test for 2nd trimester (> 20 WA)[6-8]

Benefits

- **Reassure and keep at home patients with a very low short-term risk (80% of patients).**
- **Early warning for patients who are likely to develop the first signs of PE (headache, visual disturbances, edema, abdominal pains ...).**
- **Referral of patients with a high short-term risk for early hospitalization or regular monitoring.**

The **PlGF** *(Placental Growth Factor)*, produced by the placenta, is an angiogenic factor that plays a key role in the fetoplacental vascular development.

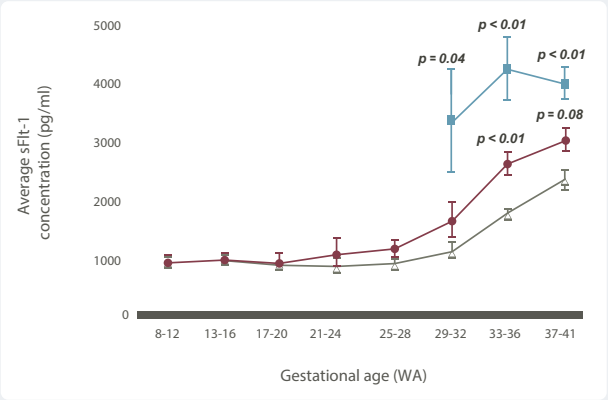
- The PlGF concentration drops abnormally low **9 to 11 weeks before the occurrence of PE.**



Controls
Patients who are likely to develop a PE
Patients with a clinical PE at time of test

SFlt-1 (soluble PlGF receptor) is an antiangiogenic factor. It captures the circulating PlGF that cannot be attached to its membrane receptor, thereby decreasing its pro-angiogenic activity.

- The PlGF concentration is abnormally elevated around **5 weeks before the occurrence of PE.**

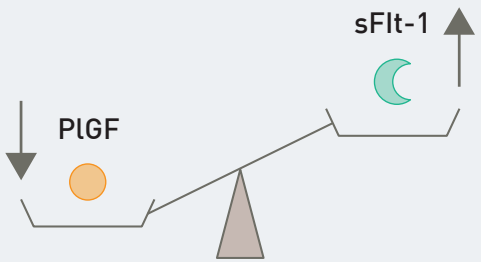


Controls
Patients who are likely to develop a PE
Patients with a clinical PE at time of test

Ratio = sFlt-1 / PlGF

The **imbalance** in sFlt-1 and PlGF concentrations is **detectable several weeks before** the clinical onset of pre-eclampsia.

The sFlt-1/PlGF ratio has a better positive predictive value (PPV) than the measurement of sFlt-1 by itself.



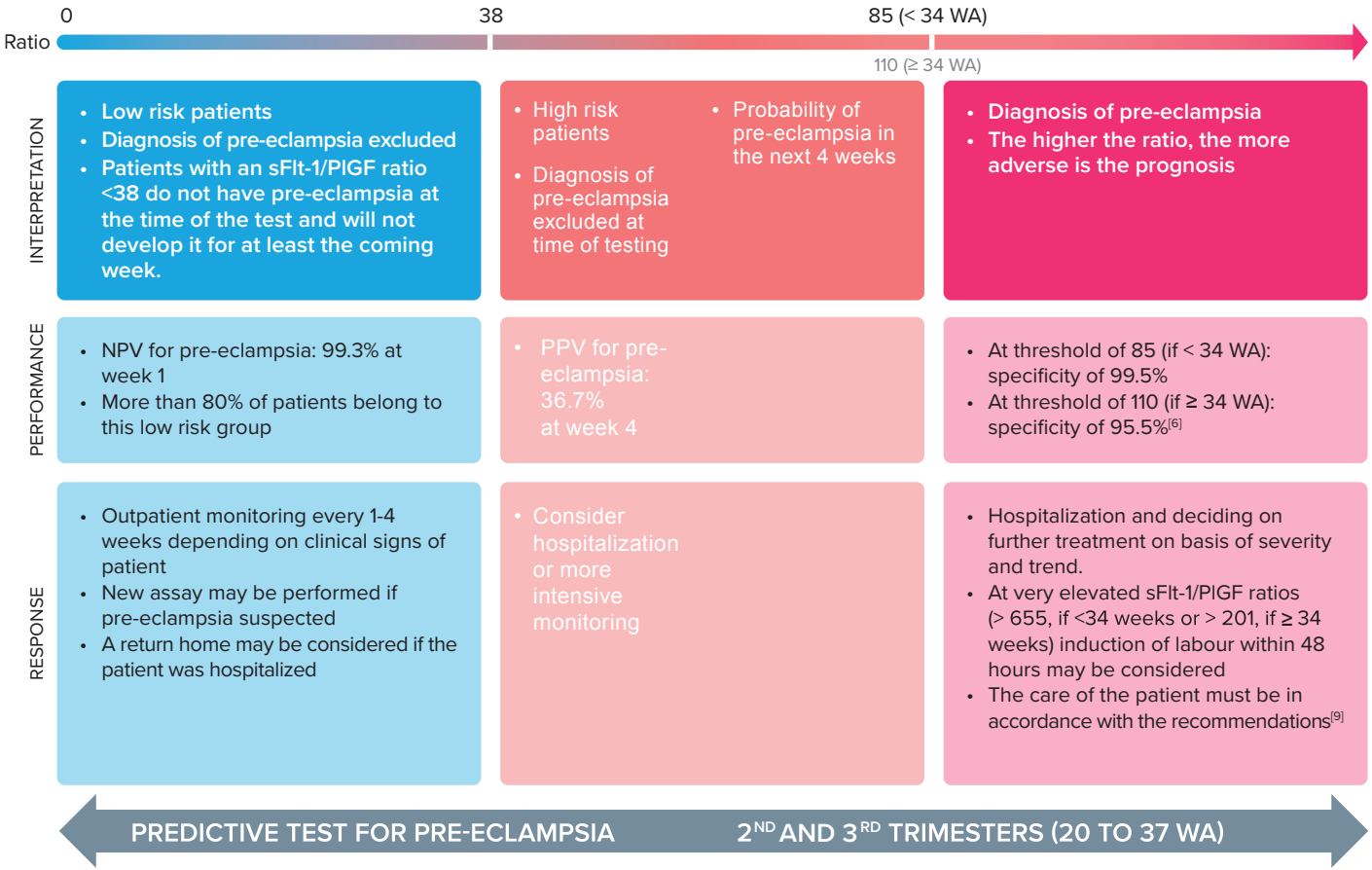
PROGNOSIS study [8]

The PROGNOSIS study is a multicentre, prospective, non-interventional, randomized, double-blind study that evaluated the short-termprediction of pre-eclampsia in pregnant women at risk of pre-eclampsia. Between December 2010 and January 2014, 1270 patientswere enrolled and 30 centres located in 14 countries participated. The results were published at the start of 2016.

sFlt-1/PlGF ratio: a decision-making aid for the clinician

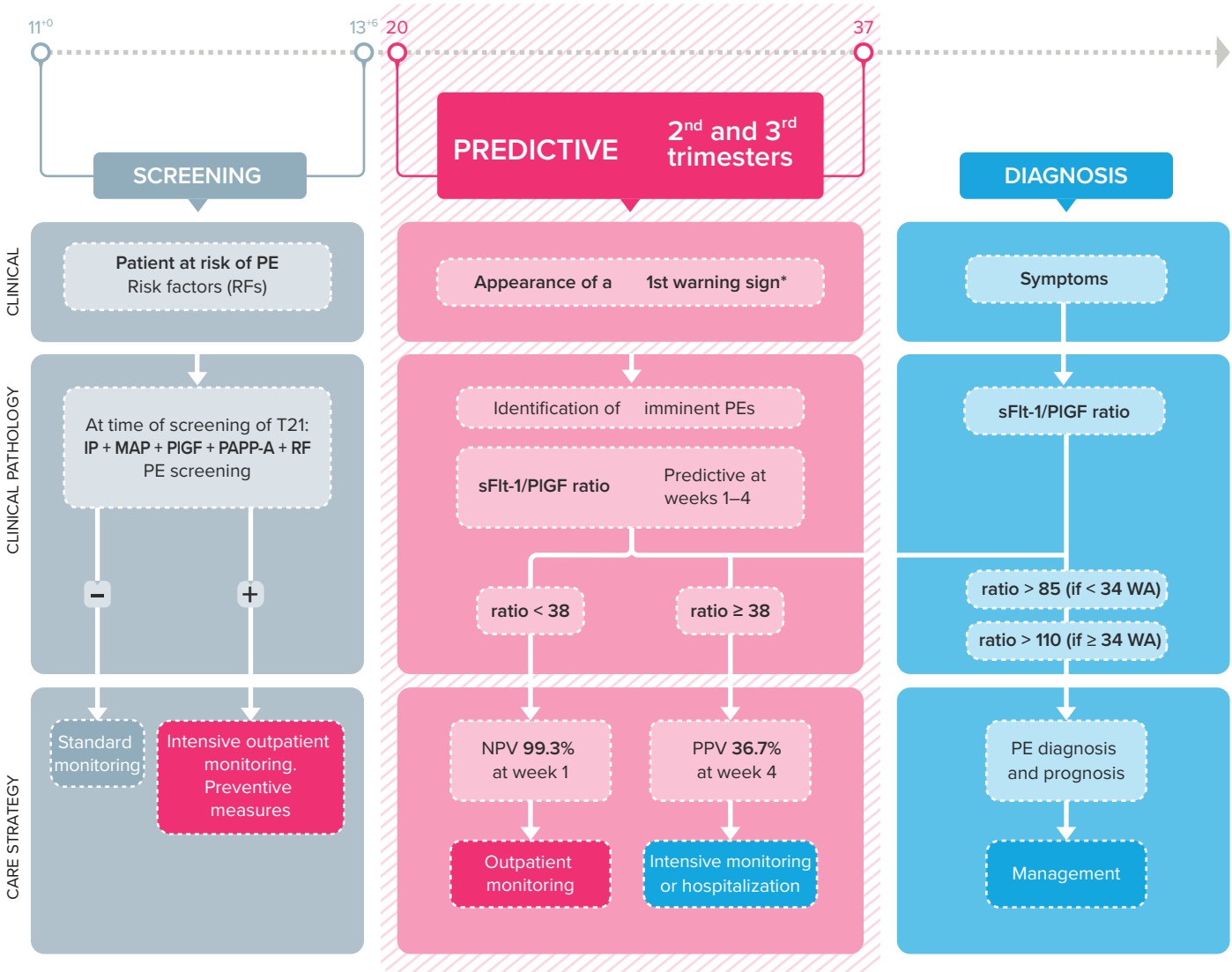
A **ratio <38** is the basis for referring women to **outpatient care** with a negative predictive value (NPV) of 99.3% at one week. A **ratio ≥ 38** flags the **need for care and hospitalization of patients** at high risk with a positive predictive value (PPV) of 36.7% at 4 weeks of developing a PE.

In the presence of a warning sign, the sFlt-1/PlGF ratio alerts the clinician to possible development of pre-eclampsia.



NEW | PREDICTIVE TEST

Strategy for use of biomarkers



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- New onset or exacerbated arterial hypertension
- New onset or exacerbated proteinuria
- Epigastric pain
- Excessive edema
- Headaches
- Visual disorders
- Sudden weight gain
- Thrombopenia (< 100 giga/L)
- Elevated hepatic enzymes
- IUGR (suspected)
- Abnormal ultrasound result for uterine arteries

In practice

For pre-eclampsia screening in 1st trimester

Recommendation

- PIGF and PAPP-A assay

Sampling

- Between 11^{+0} et 13^{+6} WA
- Blood sample: use a separate dry tube for PE screening. After removal of clot, centrifuge at high speed to separate serum.

Storage and transport

- Refrigerate (+2 °C to +8 °C)

For the pre-eclampsia predictive test

Recommendation

- sFlt-1/PlGF assays

Sampling

- Starting from 20 WA
- Blood sample (2 ml): use a separate dry tube for PE screening. After removal of the clot, centrifuge at high speed to separate the serum.

Storage and transport

- Freeze (-18 °C)

Information to be provided

- It is essential to provide pregnancy dates (date of pregnancy or crown-rump length and date of ultrasound examination between weeks 11^{+0} and 13^{+6}) and date of sample

References

1. HSE, The Diagnosis and Management of Pre-eclampsia and eclampsia clinical practice Guideline, 2013, 3:0
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4. Poon LC, Kametas NA, Maiz N, Akolekar R, Nicolaides KH, Firsttrimester prediction of hypertensive disorders in pregnancy. Hypertension 2009;53:812-8.
5. O'Gorman N *et al*. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation. Am J Obstet Gynecol 2016, in press
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7. Stepan *et al*. Opinion. Implementation of the sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia in singleton pregnancy: implications for clinical practice. Ultrasound Obstet Gynecol 2015;45:241-6
8. Zeisler H *et al*. Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. N Engl J Med. 2016;374:13-22.
9. Prise en charge multidisciplinaires des formes graves de pré-éclampsie (27 janvier 2009). Recommandations formalisées communes d'experts SFAR / CNGOF / SFMP / SFNN (www.cngof.asso.fr)

Glossary

UAD	: Doppler ultrasound of uterine arteries:
RF	: Risk factor
FP	: False positive rate
MAP	: Mean arterial pressure
PAPP-A	: *Pregnancy-Associated Plasma Protein-A*
PE	: Pre-eclampsia
PlGF	: *Placental Growth Factor*
WA	: Week of amenorrhea
sFlt-1	: *fms-like tyrosine kinase 1* (soluble fraction of type VEGF receptor (VEGF-R1))
VEGF	: Vascular Endothelial Growth Factor
PPV	: Positive predictive value
NPV	: Negative predictive value

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